

ISIS-1169

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Cook, *et al.*

Serial No.: 08/117,363



Group Art Unit: 1634

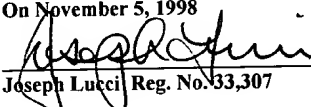
Filed: September 3, 1993

Examiner: S. Houtteman

For: AMINE-DERIVATIZED NUCLEOSIDES AND OLIGONUCLEOSIDES

I, Joseph Lucci, Registration No. 33,307 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On November 5, 1998

  
Joseph Lucci Reg. No. 33,307

Assistant Commissioner  
for Patents  
Washington, D.C. 20231

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APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

Applicants appeal the Final Rejection dated January 7, 1998, in connection with the above-identified application.

I. Real Party in Interest

Based on information supplied by Applicants and to the best of the undersigned's

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knowledge, the real party in interest in the above-identified patent application is ISIS Pharmaceuticals, Inc., a corporation of Delaware, which is the assignee of Phillip Dan Cook, Muthiah Manoharan, and Charles J. Guinosso.

## **II. Related Appeals and Interferences**

There are no other appeals or interferences known to Applicants, Applicants' legal representative, or the assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal. Applicants note, however, the pendency of Interference Nos. 104,235 and 104,401, which involve patent applications that claim priority from certain of the patent applications from which the present patent application claims priority.

## **III. Status of Claims**

Claims 1-29 are pending in this patent application. Claims 30-35 were canceled during prosecution. Of the pending claims, claims 1-4, 6-18, and 20-29 are the subject of this appeal and appear in Appendix A.

## **IV. Status of Amendments**

There were no amendments filed subsequent to the Final Rejection.

## **V. Summary of the Invention**

The present invention relates, *inter alia*, to Applicants' recognition that the activity of nucleic acids can be modulated through the use of amine-derivatized chemical compounds such as those recited in claims 1-4, 6-18, and 20-29.

It is well known that nucleic acids such as DNA and RNA direct the synthesis of cellular proteins. This synthesis entails two related processes, transcription and translation.

Transcription (also known as RNA synthesis) is the transfer of genetic information from the double-stranded DNA molecule to a single stranded RNA molecule. The RNA molecule that is synthesized is complementary to a segment of one of the two DNA strands and, therefore, is an exact copy of a segment of the other DNA strand except that any thymine residues are replaced with uracil residues. Translation, in turn, is the transfer of genetic information from a single stranded RNA molecule, in this case messenger RNA (mRNA), to an amino acid sequence of a protein chain. During translation, a cellular organelle named a "ribosome" binds to the mRNA molecule in a specific location. Transfer RNA molecules (tRNA) bring amino acids to the ribosome where they are matched to the "transcribed" message present on the mRNA. As each amino acid is brought to the ribosome, the ribosome moves further along the mRNA. A second tRNA then brings a second amino acid corresponding to the transcribed message. The second amino acid is joined to the first amino acid, forming a chain. This process repeats as the ribosome moves along the mRNA until the ribosome recognizes a signal which marks the end of the message (the termination site).

It is well known to those of skill in the art that short, single stranded DNA molecules (oligonucleotides) can be used to block translation of mRNA into a protein. Such oligonucleotides can be used to block the translation of the mRNA by the ribosome by, for example, hybridizing with (*i.e.*, binding to) the mRNA.

Applicants' claimed inventions relate, at least in part, to their recognition that modulation of nucleic acids such as mRNA and other intracellular RNAs -- as, for example, effected by short, single stranded DNA molecules -- also can be effected by the amine-derivatized chemical compounds recited in pending claims 1-4, 6-18, and 20-29.

## VI. Issues

The issue that remains for resolution in this appeal is whether the subject matter of claims 1-4, 6-18, and 20-29 is unpatentable under 35 U.S.C. § 103(a) as allegedly being obvious in view of U.S. Patent No. 4,910,300 ("the Urdea patent") in view of U.S. Patent No. 4,743,535 ("the Carrico patent"), International patent application WO 91/14696 ("the Latham reference"), and International patent application WO 92/05186 ("the Matteucci reference").

## VII. Grouping of the Claims

Applicants believe that appealed claims 1-4, 6-18, and 20-29 stand or fall together.

## VIII. Argument

There is no evidence of record indicating that those of ordinary skill would have been motivated to combine the teachings of the cited references in the manner the Office Action proposes. In fact, there is good reason to believe that those of ordinary skill would not have been motivated to make this combination. Accordingly, the rejection of claims 1-4, 6-18, and 20-29 for alleged obviousness is improper and should be withdrawn.

Although the Examiner suggests that those of ordinary skill would have been motivated to attach one of the non-terminal *internucleoside* linkages disclosed by the Matteucci reference at the terminal *2'-position* of a nucleoside in place of the terminal 2'-substituents disclosed by the Latham reference (Final Rejection at page 3), the Examiner has not identified any reason why those of ordinary skill would have been so motivated. Indeed, there is ample evidence that those of

ordinary skill in the art, when considering what terminal 2'-substituent should be appended to a given nucleoside, would not have consulted prior art (such as the Matteucci reference) relating to non-terminal internucleoside linkages. This can be seen, for example, in the cited references themselves, which define 2'-substituents and internucleoside linkages by reference to distinct, separate groups that do not contain common members. The Latham reference, for example, discloses certain groups that can be attached to the 2'-position<sup>1</sup> (*see, e.g.*, page 18, lines 3-29), but proposes an entirely different class of moieties for use as internucleoside linkages (*see, e.g.*, page 21, lines 30-36). Similarly, the Matteucci reference proposes one class of moieties for use as 2'-substituents (*see, e.g.*, page 5, lines 22-23), but an entirely different class for use as internucleoside linkages (*see, e.g.*, page 5, lines 26-33 and page 13, line 11 - page 20, line 25). These references demonstrate that persons of ordinary skill in the art regard 2'-substituents and internucleoside linkages to be distinct moieties that are not interchangeable. Accordingly, such persons, would not have been motivated to modify the teachings of the prior art in the manner proposed by the Examiner. There is simply no reason why a person of ordinary skill would have been motivated to take one of the *non-terminal*, 3'-5' *internucleoside* linkages disclosed by the Matteucci reference (such a linkage being covalently bound at both of its ends) and then attach it in a *terminal* manner at the *2'-position* (so as to be covalently bound at only one end).

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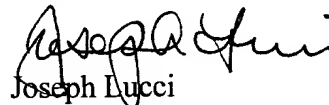
<sup>1</sup> These groups are also said to be suitable for attachment to the 5'- or 3'-*terminus*. As will be recognized, the 5'- and 3'-termini (which are at either end of an oligonucleotide) are distinguishable from the internal 5'- and 3'-positions between which internucleoside linkages typically are formed.

Given the absence of any evidence that a person of ordinary skill would have been motivated to modify the teachings of the prior art in a way that would have produced a claimed invention, much less evidence that such persons would have been impelled to make such modification, the rejection for alleged obviousness is improper and should be withdrawn. *In re Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993) ("an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would impel one skilled in the art to do what the patent applicant has done").

#### IX. Conclusion

For the foregoing reasons, Applicants submit that the inventions of claims 1-4, 6-18, and 20-29 fully comply with the requirements 35 U.S.C. § 103(a). Applicants therefore request that this patent application be remanded to the Examiner with an instruction to both withdraw the rejection for alleged obviousness and allow the appealed claims.

Respectfully submitted,



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Date: November 5, 1998

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